

## WO9858911A2: PROSTAGLANDIN AGONISTS

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**Abstract:** This invention relates to prostaglandin agonists, methods of using such prostaglandin agonists, pharmaceutical compositions containing such prostaglandin agonists and kits containing such prostaglandin agonists. The prostaglandin agonists are useful for the treatment of bone disorders including osteoporosis.

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/IB98/00866  <b>(22) International Filing Date:</b> 4 June 1998 (04.06.98)  <b>(30) Priority Data:</b> 60/050,575                      23 June 1997 (23.06.97)                      US  <b>(71) Applicant (for all designated States except US):</b> PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> CAMERON, Kimberly, O'Keefe [US/US]; 5 North Winchester Court, East Lyme, CT 06333 (US). DASILVA-JARDINE, Paul, Andrew [GY/US]; 89 Angell Street, Providence, RI 02906 (US).  <b>(74) Agents:</b> SPIEGEL, Allen, J.; c/o Green, Mark, Charles, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB) et al.		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished          upon receipt of that report.</i>
<b>(54) Title:</b> PROSTAGLANDIN AGONISTS		
<b>(57) Abstract</b>  This invention relates to prostaglandin agonists, methods of using such prostaglandin agonists, pharmaceutical compositions containing such prostaglandin agonists and kits containing such prostaglandin agonists. The prostaglandin agonists are useful for the treatment of bone disorders including osteoporosis.  <div style="text-align: right; font-family: cursive; font-size: 1.2em;">Claims?</div>		

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## PROSTAGLANDIN AGONISTS

BACKGROUND OF INVENTION

This invention relates to prostaglandin agonists, pharmaceutical  
5 compositions containing such agonists and the use of such agonists to prevent  
bone loss or restore or augment bone mass including the treatment of conditions  
which present with low bone mass in mammals, including humans.

Osteoporosis is a systemic skeletal disease, characterized by low bone  
mass and deterioration of bone tissue, with a consequent increase in bone fragility  
10 and susceptibility to fracture. In the U.S., the condition affects more than 25 million  
people and causes more than 1.3 million fractures each year, including 500,000  
spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most  
serious consequence of osteoporosis, with 5-20% of patients dying within one  
year, and over 50% of survivors being incapacitated.

15 The elderly are at greatest risk of osteoporosis, and the problem is  
therefore predicted to increase significantly with the aging of the population.  
Worldwide fracture incidence is forecasted to increase three-fold over the next 60  
years, and one study estimated that there will be 4.5 million hip fractures  
worldwide in 2050.

20 Women are at greater risk of osteoporosis than men. Women experience a  
sharp acceleration of bone loss during the five years following menopause. Other  
factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle  
and low calcium intake.

There are currently two main types of pharmaceutical therapy for the  
25 treatment of osteoporosis. The first is the use of anti-resorptive compounds to  
reduce the resorption of bone tissue.

Estrogen is an example of an anti-resorptive agent. It is known that  
estrogen reduces fractures. In addition, Black, et al. in EP 0605193A1 report that  
estrogen, particularly when taken orally, lowers plasma levels of LDL and raises  
30 those of the beneficial high density lipoproteins (HDL's). However, estrogen failed  
to restore bone back to young adult levels in the established osteoporotic skeleton.  
Furthermore, long-term estrogen therapy, however, has been implicated in a  
variety of disorders, including an increase in the risk of uterine cancer, endometrial

cancer and possibly breast cancer, causing many women to avoid this treatment. The significant undesirable effects associated with estrogen therapy support the need to develop alternative therapies for osteoporosis that have the desirable effect on serum LDL but do not cause undesirable effects.

5           A second type of pharmaceutical therapy for the treatment of osteoporosis is the use of anabolic agents to promote bone formation and increase bone mass. This class of agents is expected to restore bone to the established osteoporotic skeleton.

10           U.S. Patent No. 3,932,389, incorporated herein by reference, discloses certain tetrazolyl prostaglandin derivatives as vasodilators, bronchodilators, antiulcer and antisecretory agents.

          U.S. Patent No. 4,097,601, incorporated herein by reference, discloses selected compounds from U.S. Patent No. 3,932,389 as having utility in the treatment of bone disorders.

15           British patent number GB 1 521 688 discloses certain cyclopentanones for the production of hypotension, bronchodilation, inhibition of gastric acid secretion, healing of gastric ulcers, luteolysis and the stimulation of uterine contraction.

          U.S. Patent No. 3,980,700, incorporated herein by reference, discloses certain cyclopentanones as antibacterial agents.

20           U.S. Patent No. 4,197,407, incorporated herein by reference, discloses certain cyclopentanones as smooth muscle stimulants, arterial blood pressure lowering agents and antagonists of epinephrine-induced mobilization of free fatty acid.

          In addition to osteoporosis, approximately 20-25 million women and an  
25   increasing number of men have detectable vertebral fractures as a consequence of reduced bone mass, with an additional 250,000 hip fractures reported yearly in America alone. The latter case is associated with a 12% mortality rate within the first two years and with a 30% rate of patients requiring nursing home care after the fracture. While this is already significant, the economic and medical  
30   consequences of convalescence due to slow or imperfect healing of these bone fractures is expected to increase, due to the aging of the general population. While there are several promising therapies (bis-phosphonates, etc.) in development to prevent bone loss with age and thus reduce the probability of incurring debilitating

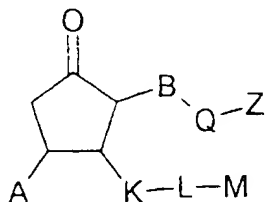
fractures, these therapies are not indicated for restoration of bone mass once the fracture has occurred.

Estrogens have been shown (Bolander et al., 38th Annual Meeting Orthopedic Research Society, 1992) to improve the quality of the healing of  
5 appendicular fractures. Therefore, estrogen replacement therapy might appear to be a method for the treatment of fracture repair. However, patient compliance with estrogen therapy is relatively poor due to its side effects, including the resumption of menses, mastodynia, an increased risk of uterine cancer, an increased  
perceived risk of breast cancer, and the concomitant use of progestins. In addition,  
10 men are likely to object to the use of estrogen treatment. Clearly the need exists for a therapy which would be beneficial to patients who have suffered debilitating bone fractures and which would increase patient compliance.

Although there are a variety of osteoporosis therapies there is a continuing need and a continuing search in this field of art for alternative osteoporosis  
15 therapies. In addition, there is a need for bone fracture healing therapies.

SUMMARY OF THE INVENTION

This invention is directed to compounds of Formula I



Formula I

- 5 prodrugs thereof and pharmaceutically acceptable salts of said compounds and prodrugs

wherein

A is hydrogen or hydroxy;

B is propylene, propenylene or propynylene;

- 10 Q is propylene,  $-\text{CH}_2\text{OCH}_2-$ , thiazolyl, pyridyl, phenyl or thienyl;

Z is carboxyl,  $(\text{C}_1-\text{C}_6)$ alkoxycarbonyl, tetrazolyl, 1,2,4-oxadiazolyl or 5-oxo-1,2,4-oxadiazolyl;

K is ethylene or ethenylene;

L is a bond or  $-\text{CO}-$ ;

- 15 M is  $-\text{Ar}$ ,  $-\text{Ar}^1-\text{V}-\text{Ar}^2$ ,  $-\text{Ar}^1-\text{S}-\text{Ar}^2$  or  $-\text{Ar}^1-\text{O}-\text{Ar}^2$  wherein

- Ar and  $\text{Ar}^1$  are either (1) each independently a fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, any of said partially saturated or fully saturated rings optionally having one or more oxo groups substituted on carbon, or
- 20
- 25

(2) each independently a fully saturated five to eight membered ring;

$\text{Ar}^2$  is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently

from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, any of said partially saturated or fully saturated rings optionally having one or more oxo groups substituted on carbon;

- 10        said Ar and Ar<sup>1</sup> moieties, when a fully unsaturated five to eight membered ring, a bicyclic ring or a tricyclic ring, and said Ar<sup>2</sup> moieties are each independently optionally substituted on carbon, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to three substituents selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently hydroxy, nitro, halo, (C<sub>1</sub>-C<sub>7</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>7</sub>)alkyl, (C<sub>2</sub>-C<sub>7</sub>)alkenyl, (C<sub>2</sub>-C<sub>7</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>4</sub>)alkanoyl, formyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C<sub>1</sub>-C<sub>4</sub>)alkyl substituted aminocarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonylamino, sulfonamido, hydroxysulfonyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonamido, amino, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, carbamoyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>)alkylcarbamoyl, cyano, thiol, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl or mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>)alkylaminosulfinyl;
- 25        R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>, when containing an alkyl, alkenyl, alkylene or alkenylene moiety, are optionally straight or branched and are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

V is a bond, -CO- or (C<sub>1</sub>-C<sub>3</sub>)alkylene optionally mono- or di-substituted independently with hydroxy or fluoro,

- provided that (1) when L is -CO-, A is hydroxy and (2) when L is a bond and M is phenyl, said phenyl is substituted with one to three substituents selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>.

A preferred group of compounds, designated the A Group, contains those compounds having the Formula I as shown above, and pharmaceutically



acceptable salts thereof, wherein L is absent, B and Q are each n-propylene and Z is carboxy, (C<sub>1</sub>-C<sub>3</sub>)alkoxycarbonyl or tetrazolyl.

A group of compounds which is preferred within the A Group, designated the B Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein A is OH.

A group of compounds which is preferred within the B Group, designated the C Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein M is thiazolyl or pyridyl optionally substituted with up to three substituents independently selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>; or M is phenyl substituted with one to three substituents independently selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>.

A group of compounds which is preferred within the C Group, designated the D Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein K is ethenylene.

A group of compounds which is preferred within the D group, designated the E Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein M is phenyl substituted with one to three groups selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>, wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected from (C<sub>1</sub> - C<sub>7</sub>) alkoxy, hydroxy, trifluoromethyl, trifluoromethoxy, halo and (C<sub>1</sub> - C<sub>6</sub>) alkyl.

A group of compounds which is preferred within the E group, designated the F Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently chloro and Z is carboxy, ethoxycarbonyl or tetrazolyl.

Especially preferred compounds within the F Group are those compounds, and pharmaceutically acceptable salts thereof, wherein said phenyl group is substituted with 3-chloro or 3,5-dichloro.

Another group of preferred compounds within the A Group, designated the G Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein A is H.

A group of compounds which is preferred within the G Group, designated the H Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein M is thiazolyl or pyridyl optionally substituted with up to three substituents independently selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>; or M is phenyl substituted with one to three substituents independently selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>.

A group of compounds which is preferred within the H Group, designated the J Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein K is ethenylene.

5 A group of compounds which is preferred within the J Group, designated the K Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein M is phenyl substituted with one to three groups selected from  $R^1$ ,  $R^2$  and  $R^3$ , wherein  $R^1$ ,  $R^2$  and  $R^3$  are independently selected from ( $C_1 - C_7$ ) alkoxy, hydroxy, trifluoromethyl, trifluoromethoxy, halo and ( $C_1 - C_6$ ) alkyl.

10 A group of compounds which is preferred within the K Group, designated the L Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein  $R^1$ ,  $R^2$  and  $R^3$  are independently chloro, fluoro or trifluoromethyl and Z is carboxy, ethoxycarbonyl or tetrazolyl.

Especially preferred compounds within the K Group are *trans*-7-(2-(2-(3,5-bis-trifluoromethyl-phenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoic acid; *trans*-7-(2-(2-(4-chloro-3-trifluoromethyl-phenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoic acid; *trans*-7-(2-(2-(3,5-dichlorophenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoic acid; *trans*-7-(2-(2-(3-chlorophenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoic acid; *trans*-7-(2-oxo-5-(2-(3-trifluoromethyl-phenyl)-vinyl)-cyclopentyl)-heptanoic acid; and *trans*-7-(2-(2-(4-fluoro-phenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoic acid; and pharmaceutically  
20 acceptable salts thereof.

Another group of compounds which is preferred within the L Group, designated the M Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein Z is carboxy.

25 An especially preferred compound within the M Group is the compound wherein M is 3,5-bis-trifluoromethylphenyl.

Another especially preferred compound within the M Group is the compound wherein M is 4-chloro-3-trifluoromethylphenyl.

Another especially preferred compound within the M Group is the compound wherein M is 3,5-dichlorophenyl.

30 Another especially preferred compound within the M Group is the compound wherein M is 3-chlorophenyl.

Another especially preferred compound within the M Group is the compound wherein M is 3-trifluoromethylphenyl.

Another especially preferred compound within the M Group is the compound wherein M is 4-fluorophenyl.

Other especially preferred compounds within the K Group are ethyl *trans*-7-(2-(2-(3,5-bis-trifluoromethyl-phenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoate; ethyl *trans*-7-(2-(2-(4-chloro-3-trifluoromethyl-phenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoate; ethyl *trans*-7-(2-(2-(3,5-dichlorophenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoate; ethyl *trans*-7-(2-(2-(3-chlorophenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoate; ethyl *trans*-7-(2-oxo-5-(2-(3-trifluoromethyl-phenyl)-vinyl)-cyclopentyl)-heptanoate; and ethyl *trans*-7-(2-(2-(4-fluoro-phenyl)-vinyl)-5-oxo-cyclopentyl)-heptanoate; and pharmaceutically acceptable salts thereof.

Another group of compounds which is preferred within the L Group, designated the N Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein Z is ethoxycarbonyl.

An especially preferred compound within the N Group is the compound wherein M is 3,5-bis-trifluoromethylphenyl.

Another especially preferred compound within the N Group is the compound wherein M is 4-chloro-3-trifluoromethylphenyl.

Another especially preferred compound within the N Group is the compound wherein M is 3,5-dichlorophenyl.

Another especially preferred compound within the N Group is the compound wherein M is 3-chlorophenyl.

Another especially preferred compound within the N Group is the compound wherein M is 3-trifluoromethylphenyl.

Another especially preferred compound within the N Group is the compound wherein M is 4-fluorophenyl.

Other especially preferred compounds within the K Group are *trans*-3-(2-(3,5-bis-trifluoromethyl-phenyl)-vinyl)-2-(6-(2H-tetrazol-5-yl)-hexyl)-cyclopentanone; *trans*-3-(2-(4-chloro-3-trifluoromethylphenyl)-vinyl)-2-(6-(2H-tetrazol-5-yl)-hexyl)-cyclopentanone; *trans*-3-(2-(3,5-dichloro-phenyl)-vinyl)-2-(6-(2H-tetrazol-5-yl)-hexyl)-cyclopentanone; *trans*-3-(2-(3-chloro-phenyl)-vinyl)-2-(6-(2H-tetrazol-5-yl)-hexyl)-cyclopentanone; *trans*-3-(2-(3-trifluoromethyl-phenyl)-vinyl)-2-(6-(2H-tetrazol-5-yl)-hexyl)-cyclopentanone; and *trans*-3-(2-(4-fluoro-phenyl)-vinyl)-2-(6-

(2H-tetrazol-5-yl)-hexyl)-cyclopentanone; and pharmaceutically acceptable salts thereof.

Another group of compounds which is preferred within the L Group, designated the P Group, contains those compounds wherein Z is tetrazolyl.

5        An especially preferred compound within the P Group is the compound wherein M is 3,5-bis-trifluoromethylphenyl.

Another especially preferred compound within the P Group is the compound wherein M is 4-chloro-3-trifluoromethylphenyl.

10       Another especially preferred compound within the P Group is the compound wherein M is 3,5-dichlorophenyl.

Another especially preferred compound within the P Group is the compound wherein M is 5-chlorophenyl.

Another especially preferred compound within the P Group is the compound wherein M is 3-trifluoromethylphenyl.

15       Another especially preferred compound within the P Group is the compound wherein M is 4-fluorophenyl.

Another preferred group of compounds of Formula I, designated the Q Group, contains those compounds, and pharmaceutically acceptable salts thereof, having the Formula I as shown above wherein L is -CO-, B and Q are each n-  
20       propylene and Z is carboxy, (C<sub>1</sub>-C<sub>3</sub>)alkoxycarbonyl or tetrazolyl.

A group of compounds which is preferred within the Q Group, designated the S Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein A is OH.

25       A group of compounds which is preferred within the S Group, designated the T Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein M is thiazolyl or pyridyl optionally substituted with up to three substituents independently selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>; or M is phenyl substituted with one to three substituents independently selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>.

30       A group of compounds which is preferred within the T Group, designated the U Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein K is ethenylene.

A group of compounds which is preferred within the U Group, designated the V Group, contains those compounds, and pharmaceutically acceptable salts

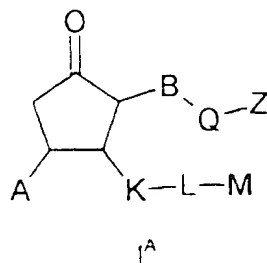
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thereof, wherein M is phenyl substituted with one to three groups selected from  $R^1$ ,  $R^2$  and  $R^3$ , wherein  $R^1$ ,  $R^2$  and  $R^3$  are independently selected from ( $C_1 - C_7$ ) alkoxy, hydroxy, trifluoromethyl, trifluoromethoxy, halo and ( $C_1 - C_6$ ) alkyl.

A group of compounds which is preferred within the V Group, designated the X Group, contains those compounds, and pharmaceutically acceptable salts thereof, wherein  $R^1$ ,  $R^2$  and  $R^3$  are independently chloro and Z is carboxy, ethoxycarbonyl or tetrazolyl.

Especially preferred compounds within the X Group are those compounds, and pharmaceutically acceptable salts thereof, wherein said phenyl group is substituted with 3-chloro or 3,5-dichloro.

This invention is also directed to methods for augmenting and maintaining bone mass and preventing further bone loss in vertebrate, e.g., a mammal, comprising administering to a mammal a therapeutically effective amount of a compound of Formula I<sup>A</sup>



prodrugs thereof or pharmaceutically acceptable salts of said compounds or said prodrugs wherein

- A is hydrogen or hydroxy;
- B is propylene, propenylene or propynylene;
- Q is propylene,  $-CH_2OCH_2-$ , thiazolyl, pyridyl, phenyl or thienyl;
- Z is carboxyl, ( $C_1 - C_6$ )alkoxycarbonyl, tetrazolyl, 1,2,4-oxadiazolyl or 5-oxo-1,2,4-oxadiazolyl;
- K is ethylene or ethenylene;
- L is a bond or  $-CO-$ ;
- M is  $-Ar$ ,  $-Ar^1-V-Ar^2$ ,  $-Ar^1-S-Ar^2$  or  $-Ar^1-O-Ar^2$  wherein
- $Ar$ ,  $Ar^1$  and  $Ar^2$  are each independently a fully saturated, partially unsaturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a

bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or, a tricyclic ring consisting of three fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, any of said partially saturated or fully saturated rings optionally having one or more oxo groups substituted on carbon,

5 said Ar, Ar<sup>1</sup> and Ar<sup>2</sup> moieties are each independently optionally substituted on carbon, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to three substituents independently selected from R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are hydroxy, nitro, halo, (C<sub>1</sub>-C<sub>7</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>7</sub>)alkyl, (C<sub>2</sub>-C<sub>7</sub>)alkenyl, (C<sub>2</sub>-C<sub>7</sub>)alkynyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>4</sub>)alkanoyl, formyl, (C<sub>1</sub>-C<sub>8</sub>)alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C<sub>1</sub>-C<sub>4</sub>)alkyl substituted aminocarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonylamino, sulfonamido, hydroxysulfonyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonamido, amino, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, carbamoyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>)alkylcarbamoyl, cyano, thiol, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl or mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>)alkylaminosulfinyl; R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>, when containing an alkyl, alkenyl, alkylene or alkenylene moiety, are optionally straight or branched and are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

25 V is a bond, -CO- or (C<sub>1</sub>-C<sub>3</sub>)alkylene optionally mono- or di-substituted independently with hydroxy or fluoro.

This invention is also directed to methods for treating vertebrates, e.g., a mammal, having a condition which presents with low bone mass comprising administering to vertebrate, e.g., a mammal, having a condition which presents with low bone mass a therapeutically effective amount of a compound of Formula I<sup>A</sup> above or a pharmaceutically acceptable salt or prodrug thereof. Preferably post-menopausal women and men over the age of 60 are treated. Also included are

individuals regardless of age who have significantly reduced bone mass, i.e., greater than or equal to 1.5 standard deviations below young normal levels.

Yet another aspect of this invention is directed to methods for treating osteoporosis, bone fractures, osteotomy, bone loss associated with periodontitis, or prosthetic ingrowth in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal suffering from osteoporosis, bone fracture, osteotomy, bone loss associated with periodontitis, or prosthetic ingrowth an osteoporosis, bone fracture, osteotomy, bone loss associated with periodontitis, or prosthetic ingrowth treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for treating osteoporosis in vertebrate, e.g., a mammal (including a human being), by comprising administering to vertebrate, e.g., a mammal suffering from osteoporosis an osteoporosis treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to method for treating osteotomy bone loss in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g. a mammal suffering from an osteotomy bone loss an osteotomy bone loss treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof. In one aspect the Formula I<sup>A</sup> compound is applied locally to a site of osteotomy.

Yet another aspect of this invention is directed to methods for treating alveolar bone loss in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal suffering from an alveolar bone loss an alveolar bone loss treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for treating bone loss associated with periodontitis in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., mammal suffering from bone loss associated with periodontitis a bone loss associated with periodontitis treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for treating childhood idiopathic bone loss in vertebrate, e.g., a mammal comprising administering to a child suffering from childhood idiopathic bone loss a childhood idiopathic bone loss treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for treating "secondary osteoporosis", which includes glucocorticoid-induced osteoporosis, hyperthyroidism-induced osteoporosis, immobilization-induced osteoporosis, heparin-induced osteoporosis or immunosuppressive-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), by administering to vertebrate, e.g., a mammal suffering from "secondary osteoporosis" a "secondary osteoporosis" treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for treating glucocorticoid-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal suffering from glucocorticoid-induced osteoporosis a glucocorticoid-induced osteoporosis treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for treating hyperthyroidism-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal suffering from hyperthyroidism-induced osteoporosis a hyperthyroidism-induced osteoporosis treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for treating immobilization-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal suffering from immobilization-induced osteoporosis a immobilization-induced osteoporosis treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.



Yet another aspect of this invention is directed to methods for treating heparin-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal suffering from heparin-induced osteoporosis a heparin-induced osteoporosis treating amount of a  
5 Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for treating immunosuppressive-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal suffering from immunosuppressive-induced osteoporosis an immunosuppressive-induced  
10 osteoporosis treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for treating a bone fracture in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal suffering from a bone fracture a bone  
15 fracture treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof. In one aspect of this invention for treating a bone fracture the Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof is applied locally to the site of bone fracture. In another aspect of this invention the Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or  
20 prodrug thereof is administered systemically.

Yet another aspect of this invention is directed to methods for enhancing bone healing following facial reconstruction or maxillary reconstruction or mandibular reconstruction in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal which has  
25 undergone facial reconstruction or maxillary reconstruction or mandibular reconstruction a bone enhancing amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof. In one aspect of this method the Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof is applied locally to the site of bone reconstruction.

30 Yet another aspect of this invention is directed to methods for treating prosthetic ingrowth in vertebrate, e.g., a mammal (including a human being), comprising administering to vertebrate, e.g., a mammal suffering from prosthetic

ingrowth a prosthetic ingrowth treating amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for inducing vertebral synostosis in vertebrate, e.g., a mammal (including a human being),  
5 comprising administering to vertebrate, e.g., a mammal undergoing surgery for vertebral synostosis a therapeutically effective amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for enhancing long bone extension in vertebrate, e.g., a mammal (including a human being),  
10 comprising administering to vertebrate, e.g., a mammal suffering from an insufficiently sized long bone a long bone enhancing amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

Yet another aspect of this invention is directed to methods for strengthening a bone graft in vertebrate, e.g., a mammal (including a human being),  
15 comprising administering to vertebrate, e.g., a mammal in receipt of a bone graft a bone graft strengthening amount of a Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof. In one aspect of this method the Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof is applied locally to the site of the bone graft.

20 A preferred dosage is about 0.001 to 100 mg/kg/day of the Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof. An especially preferred dosage is about 0.01 to 10 mg/kg/day of the Formula I<sup>A</sup> compound or a pharmaceutically acceptable salt or prodrug thereof.

This invention is also directed to pharmaceutical compositions which  
25 comprise a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the augmentation of bone mass which comprise a bone mass augmenting amount of a  
30 compound of Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of a condition which presents with low bone mass in vertebrate, e.g., a

mammal (including a human being), which comprise a low bone mass condition treating amount of a compound of Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

5 This invention is also directed to pharmaceutical compositions for the treatment of osteoporosis, bone fractures, osteotomy bone loss, bone loss associated with periodontitis, or prosthetic ingrowth in vertebrate, e.g., a mammal (including a human being), which comprises a therapeutically effective amount of a compound of Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

10 This invention is also directed to pharmaceutical compositions for the treatment of "secondary osteoporosis", which includes glucocorticoid-induced osteoporosis, hyperthyroidism-induced osteoporosis, immobilization-induced osteoporosis, heparin-induced osteoporosis or immunosuppressive-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), which  
15 comprise a "secondary osteoporosis" treating amount of a compound of Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of osteoporosis in vertebrate, e.g., a mammal (including a human being),  
20 which comprise an osteoporosis treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for enhancing bone fracture healing in vertebrate, e.g., a mammal (including a human  
25 being), which comprise a bone fracture treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of osteotomy bone loss in vertebrate, e.g., a mammal (including a  
30 human being), which comprise an osteotomy bone loss treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of alveolar bone loss in vertebrate, e.g., a mammal (including a human being), which comprise an alveolar bone loss treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and  
5 a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of childhood idiopathic bone loss in a child which comprises a childhood idiopathic bone loss treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically  
10 acceptable carrier.

This invention is also directed to pharmaceutical compositions for the augmentation of bone healing following facial reconstruction or maxillary reconstruction or mandibular reconstruction in vertebrate, e.g., a mammal (including a human being), which comprise a bone healing amount of a compound  
15 of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of bone loss associated with periodontitis in vertebrate, e.g., a mammal (including a human being), which comprise a bone loss associated with  
20 periodontitis treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of prosthetic ingrowth in vertebrate, e.g., a mammal (including a human  
25 being), which comprise a prosthetic ingrowth treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for inducing vertebral synostosis in vertebrate, e.g., a mammal (including a human being),  
30 which comprise a therapeutically effective amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the augmentation of long bone extension in vertebrate, e.g., a mammal (including a human being), which comprise bone mass augmentation treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of glucocorticoid-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), which comprise a glucocorticoid-induced osteoporosis treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of hyperthyroidism-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), which comprise a hyperthyroidism-induced osteoporosis treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of immobilization-induced osteoporosis in vertebrate, e.g., a mammal (including a human being), which comprise an immobilization-induced osteoporosis treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of heparin-induced osteoporosis in vertebrate, e.g., a mammal (including a human being) which comprise a heparin-induced osteoporosis treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of immunosuppressive-induced osteoporosis in vertebrate, e.g., a mammal (including a human being) which comprise an immunosuppressive-induced osteoporosis treating amount of a compound of the Formula I above or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.